

Fast-Track Communication

USA600 (ST45) Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infections in Urban Detroit^{▽†}

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Methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as a major source of invasive infections, implicated in 18,000 deaths annually (9). Mortality rates of 20 to 30% for patients with MRSA bloodstream infections (BSIs) have been reported, with a recent study, spanning 15 years, reporting a mortality rate of approximately 28% (11, 12, 17). Recently, we reported 60% mortality for a small number of MRSA BSIs caused by the USA600 strain type, suggesting that this strain may have unique virulence characteristics (5). USA600, or ST45, first reported as an epidemic strain spreading throughout Germany and the Netherlands in the last decade, has not been associated previously with serious infection (19–21). Given our preliminary findings, we investigated a series of consecutive cases of USA600 MRSA BSI to describe patient-, treatment-, and strain-related characteristics of the infections.

Pulsed-field gel electrophoresis (PFGE) analysis of 420 consecutive MRSA bloodstream isolates was performed, and 16 patients with USA600 MRSA BSIs were identified between July 2005 and July 2008 at a 900-bed tertiary care hospital in Detroit, MI (Fig. 1). During the study period, 65% of all *S. aureus* infections were caused by MRSA. The source of the BSI was identified by chart review using a combination of clinical and laboratory findings and other diagnostic tests according to CDC definitions (7). Epidemiologic classification was conducted based on the presence or absence of health care risk factors and determination of whether the infection was community or hospital acquired, as described previously (8a).

The Acute Physiology and Chronic Health Evaluation II (APACHE II) score was calculated for each patient upon presentation of infection (10). Thirty-day mortality was defined as mortality occurring within the 30 days following collection of the index culture sample. Microbiologic failure was defined by the growth of MRSA in a blood culture ≥ 10 days after collection of the index culture sample, while the patient was still on therapy. Clinical failure was defined by 30-day mortality and/or microbiologic failure. According to similar definitions, the overall clinical failure rate for patients with MRSA BSIs at our institution during the study period was 23% (5).

Each USA600 isolate underwent PFGE, staphylococcal cassette chromosome *mec* element (SCC*mec*), and *agr* typing and testing for Panton-Valentine leukocidin (PVL) as described previously (3, 4). *In vitro* susceptibility testing was performed according to standards set by the Clinical and Laboratory Standards Institute (4). Vancomycin MICs were determined by Etest (bioMérieux, Durham, NC) and manual broth microdilution (BMD) (4). Vancomycin minimal bactericidal concentrations (MBCs) were determined using previously established methods (4, 14), and vancomycin tolerance was defined by an MBC/MIC ratio of at least 1:32 after 24 h of incubation. Isolates were tested for the heterogeneous vancomycin-intermediate *S. aureus* (hVISA) phenotype by using the macrodilution Etest (MET; bioMérieux, Durham, NC) as described previously (22). Isolates positive for the hVISA phenotype by this method underwent population analysis as described previously

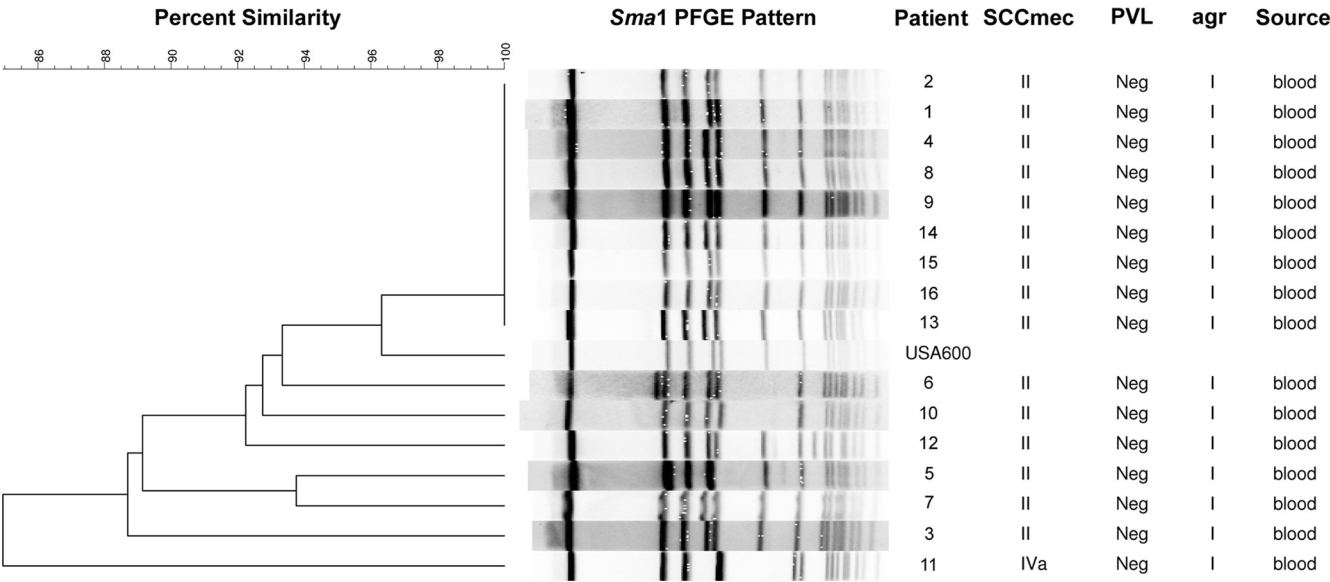


FIG. 1. PFGE patterns for the USA600 MRSA isolates.

TABLE 1. Characteristics and outcomes of USA600 MRSA BSIs^a

Patient no.	Patient age (yr), sex	Source of BSI	APACHE II score	Treatment(s) (day[s]) ^b	DOB (days)	V MIC (μg/ml) for infecting strain by Etest	V MIC (μg/ml) for infecting strain by BMD	V MBC (μg/ml) for infecting strain	Infecting strain identified as V tolerant	Infecting strain identified as hVISA by:		Outcome for patient/comments
										MET	POP	
1	56, M	Pneumonia	16	V (3–18)	1	2	0.5	0.5	No	Yes	Yes	Died (day 45)
2	60, F	Endocarditis	24	V (1–11)	5	2	1	2	No	Yes	Yes	Died (day 11)
3	86, M	Pneumonia	22	V+T (1–6), V (6–8)	1	1.5	0.5	≥32	Yes	No	NT	Died (day 8)
4	75, F	Infected graft	20	V+G (1–6), V (6–42)	4	1.5	0.5	≥32	Yes	Yes	No	Had graft removed on day 6; died (day 100)
5	41, F	Unknown	NA	NA (patient was dead on arrival at emergency room)	NA	1.5	0.5	16	Yes	Yes	No	Died (day 1)
6	89, F	Genitourinary system	32	V (2–3)	1	2	0.5	≥32	Yes	Yes	No	Withdrawn from care; died (day 8)
7	83, F	Pneumonia	38	V+T (1), C (1–2)	1	1.5	0.5	≥32	Yes	No	NT	Died (day 2)
8	77, F	Skin/wound	18	V (1–6)	1	2	0.5	0.5	No	No	NT	Died (day 6)
9	54, M	Endocarditis	23	V (1–10)	13	2	0.5	≥32	Yes	Yes	No	Experienced microbiologic failure; died (day 13)
10	44, F	Catheter	20	L+G (1–5), D (5–7), V (7–38)	1	1.5	0.5	0.5	No	No	NT	Treated successfully
11	98, F	Genitourinary system	14	L (1–3), V (3–38)	25	1.5	0.5	0.5	No	No	NT	Experienced microbiologic failure; died (day 62)
12	55, F	Skin/wound	14	V (2–15), TS (4–7)	11	1.5	0.5	≥32	Yes	Yes	Yes	Experienced microbiologic failure
13	65, M	Osteomyelitis	19	V (1–4), D (4–22), R (8–26), G (10–14), V (26–29), L (29–70)	18	1.5	0.5	≥32	Yes	No	NT	Experienced microbiologic failure
14	62, M	Infected pacemaker	13	D (1–8), R (1–4), TS (4–8)	7	3	2	2	No	Yes	Yes	Had pacemaker removed on day 7; died (day 9)
15	38, F	LVAD	12	V (1–10), D (10–13), R (8–13), G (8–13) ^c	258	1.5	0.5	0.5	No	No	NT	Experienced microbiologic failure; died (day 258)
16	34, F	Skin/wound	12	V (1–14)	1	1.5	0.5	≥32	Yes	No	NT	Treated successfully

^a Abbreviations: DOB, duration of bacteremia; POP, population analysis; NA, not applicable; NT, not tested; LVAD, left ventricular assist device; V, vancomycin; T, tobramycin; G, gentamicin; C, clindamycin; L, linezolid; D, daptomycin; TS, TMP-SMX; and R, rifampin.

^b Of 14 patients treated with vancomycin, 8 did not have serum vancomycin concentrations recorded (5 were on hemodialysis, 2 received treatment for <48 h, and data for 1 were not available). The initial (≤48-h) vancomycin serum troughs of the six remaining patients were 10 to 15 μg/ml (*n* = 4) and >15 μg/ml (*n* = 2). The definitive (>48-h) vancomycin serum troughs were 10 to 15 μg/ml (*n* = 1) and >15 μg/ml (*n* = 4); data for the remaining patient (*n* = 1) were not available. Numbers in parentheses are days postpresentation on which treatment was received.

^c Antibiotics from the first hospitalization are reported in the table. The patient was treated consecutively for 258 days with the following agents: vancomycin, rifampin, TMP-SMX, linezolid, and quinupristin-dalfopristin.

(6). Each method was performed in duplicate to confirm findings.

Clinical characteristics, therapy approaches, outcomes, and vancomycin susceptibility results are reported in Table 1. Thirty-day mortality, microbiologic failure, and clinical failure rates were 50, 31, and 75%, respectively. The majority (69%) of patients were female, and patients had a mean age (\pm standard deviation [\pm SD]) of 64 (\pm 19) years and a mean (\pm SD) APACHE II score of 20 (\pm 7) points at presentation. Comorbid conditions included diabetes (in 63% of patients), cardiovascular disease (69%), kidney disease (19%), a condition requiring hemodialysis (31%), liver disease (6%), a neurologic condition (32%), chronic obstructive lung disease (25%), malignancy (6%), immunosuppression (25%), and HIV infection (6%). Other conditions and factors present at baseline were acute renal failure (44%), previous hospital admission (56%), a history of surgery within 30 days (19%), nursing home residence (38%), and intravenous drug abuse (0%). Antimicrobials to which patients had been exposed in the previous 90 days included any (for 56% of patients), vancomycin (25%), fluoroquinolone (25%), a beta-lactam (19%), cephalosporin (13%), linezolid (13%), trimethoprim-sulfamethoxazole (TMP-SMX) (13%), an aminoglycoside (13%), and a macrolide (13%). Epidemiologic classifications of infections were community acquired (6%), health care-associated community acquired (75%), and hospital onset (19%).

None of the USA600 isolates were susceptible to clindamycin or erythromycin, 60% were susceptible to TMP-SMX, and 75% were susceptible to gentamicin. All isolates were susceptible *in vitro* to vancomycin by BMD, whereas one isolate was intermediate by Etest. For the majority (53%) of isolates, the vancomycin MBC was ≥ 32 μ g/ml, and 60% were tolerant for vancomycin. Fifty percent of USA600 MRSA isolates tested positive for the hVISA phenotype by the MET method. Four of these 8 isolates demonstrated the hVISA phenotype by population analysis. Molecular analysis revealed that 15 strains had SCCmec type II and *agr-1* and that one isolate had SCCmec type IVa and *agr-1*. All isolates were PVL negative.

This initial report describes a series of BSIs caused by USA600 MRSA. Although USA600 MRSA BSI was uncommon, we found high rates of mortality and clinical failure relative to previously reported outcomes for MRSA BSI (11, 12, 17). This case sample was not adequate to evaluate the effects of different antimicrobial strategies or the contribution of vancomycin serum trough concentrations in serum. However, most patients were treated with vancomycin, a drug to which half of the isolates were heteroresistant by MET, which could partially explain the poor outcomes. A previous case series study reported a rate of mortality from hVISA infection of approximately 40%, attributed mainly to two PFGE strain types, neither of which was USA600 (8). Another hospital in the Detroit area reported a mortality rate of 33% for hVISA BSIs, which was not significantly different from that for the non-hVISA BSIs (13). This pattern was also shown in a study of a small series of infective endocarditis cases, which reported a mortality rate of 42% for hVISA infections compared to 35% for non-hVISA infections (2). In our study, 63% of the hVISA-infected patients died within 30 days compared to 38% of the non-hVISA-infected patients. This finding suggests that other unique factors may be involved in USA600 BSIs. We found discordance in testing by MET and population analysis, which is consistent with a recent evaluation demonstrating that only 64% of isolates positive by MET were confirmed to be positive by population analysis (15). The optimal method to test for the

hVISA phenotype is unclear, although population analysis is considered to be the "gold standard."

The first reports of vancomycin-resistant *S. aureus* (VRSA) and 8 of 10 known cases of VRSA infection involved patients in the Detroit area. Recently, USA600 MRSA isolates with the hVISA phenotype were obtained from children in Detroit in a study in which 2 of 3 USA600 MRSA infections were caused by hVISA (1). Understanding the emergence of potentially novel strains in Detroit may have important implications for other geographic areas. In the present series of cases, USA600 isolates accounted for less than 5% of all BSI MRSA isolates. However, experience from Europe and Canada demonstrates that this strain has profound ability for widespread dissemination (16, 19, 20). USA600 is clonally related to the Berlin strain of MRSA (ST45), which spread throughout Germany (20), the Netherlands (19), and Ontario, Canada (16), over the last decade. Despite this, the prevalence of colonization with USA600 MRSA remains low in the United States (18), and reported infections with USA600 remain relatively infrequent. In order to fully understand the impact of USA600 MRSA both within and outside the Detroit area, these findings need confirmation in a larger comparative evaluation of BSI and possibly other types of infection.

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This study was consistent with the principles of the Declaration of Helsinki and was approved by the institutional review board at Henry Ford Hospital (under IRB no. 5536), which provided a waiver of informed patient consent due to the nature of the study.

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